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Asymmetric Synthesis of 3,6- Disubstituted Dioxopiperazines with Potential Siderophore Properties

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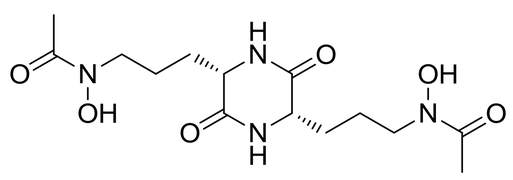
Concept and Context

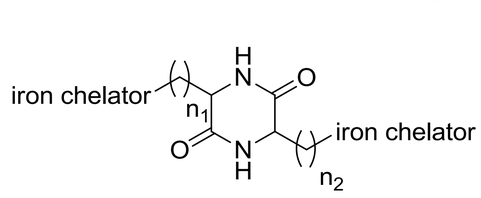
Antibiotic resistance is an emerging disease and a real problem of health. Resistance of Gram negative bacteria such as *Acinetobacter baumannii* or *Escherichia coli* to conventional antibiotic lead to therapeutic failure and requires new antibiotherapy. The use of the iron transport systems is one of the most promising strategies to overcome this resistance phenomenon. Indeed, iron is essential for the survival of the microorganisms and the exploitation of these specific routes allows the transport of ferric ion into the bacteria *via* ferric siderophore complexes.

These systems can allow the introduction of antibacterial agents (conjugates antibiotic-siderophore)[1] or toxic complexes (gallium complexes)[2] into the bacteria to kill them. Rhodotorulic acid (**RA**) is a siderophore recognised by the Fhu receptor expressed by *Acinetobacter baumannii* and *Escherichia coli*. This dioxopiperazine possesses two hydroxamates as iron ligands and two asymmetric centers with *S*,*S* configuration. This spatial orientation is essential for the recognition of the iron-siderophore complex by the Fhu receptor.

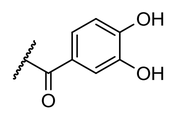
We have previously reported the asymmetric synthesis of 3-substituted 2-oxopiperazines.[3] Some ways to obtain **RA** have been described[4] but the one we propose now should be more efficient. Indeed, it is a convergent strategy which could lead quickly to the synthesis of **RA** and 3,6-disubstituted analogues of this siderophore through two successive asymmetric alkylations of a key-intermediate carrying two selective cleavable chiral inductors. These compounds will be connected to an antibiotic to test their antibacterial properties and to determine the most efficient according to the nature of the ligands and the absolute configuration of the stereogenic centers.



RA

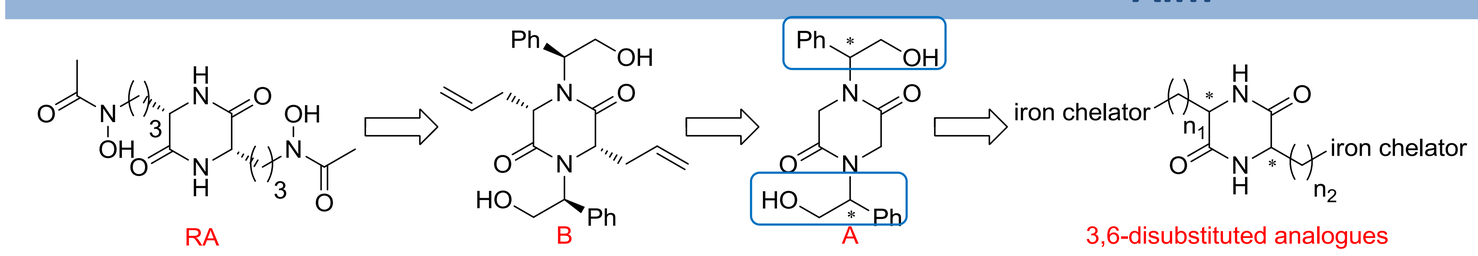


n_1,n_2 = 1 - 4
iron chelator = -N(OH)$COCH_3$, CONHOH,



3,6-disubstituted analogues

Aim



Way 1

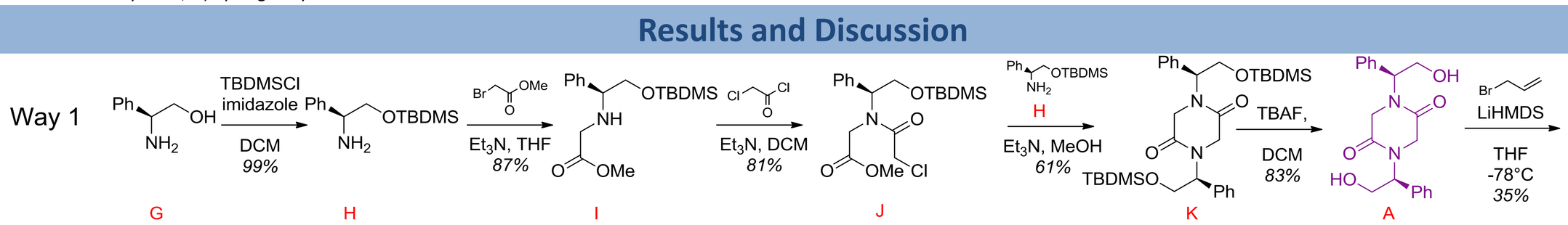
Way 2

To obtain **RA**, our first strategy (Way 1) is based on the key-intermediate **A** stereoselective dialkylation using allyl bromide. The chiral inductors allow the control of the dialkylation, leading to **B**. Then the chiral moieties are cleaved by Birch type reduction. An hydroboration followed by Mitsunobu reaction, deprotection and an acetylation lead to the formation of the hydroxamate group. Finally, an hydrogenolysis gives **RA.** Intermediate **A** can also give **RA** 3,6-disubstituted analogues by modification of : (i) the nature of the iron chelator, (ii) the length of the carbon chain and (iii) the absolute configuration of the stereogenic centers.

Our second strategy use (Way 2) glutamic acid as chiral building block. An intramolecular cyclisation afford pyroglutamic acid **D**. Two units of pyroglutamic acid **D** are coupled to form the dioxopiperazine ring. Then, the pyrrolidine cycles of **E** are opened in presence of sulfuric acid and the acids obtained are esterified with methanol.

The protection of the amides in presence of Boc_2O followed by the reduction of the ester into alcohol affords the diol **F**. To form the hydroxamates, the strategy as the way 1 is applied : i) Mitsunobu reaction , 2) deprotection and acetylation, iii) hydrogenolysis

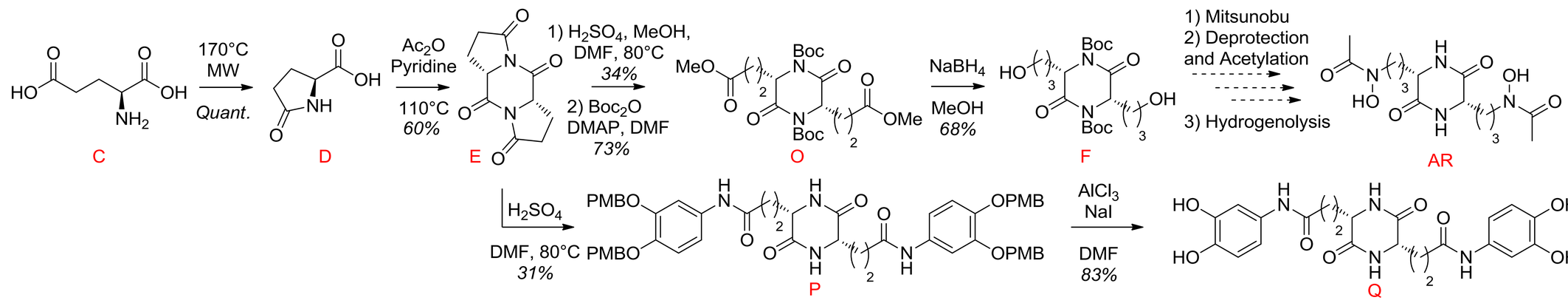
Results and Discussion



$[\alpha]_D^{22}$= +104 (c 0,58; AcOEt)
ed > 95%

$[\alpha]_D^{22}$= +51 (c 0,12; H_2O)
ed > 95%

RA should be obtained in eleven steps (Way 1) from the *S*-phenylglycinol **G**. At this time, we have synthesized the dioxopiperazine **A** in 35% global yield : i) protection of the phenylglycinol **C** with TBDMSCl, ii) alkylation in presence of methyl 2-bromoacetate affords the secondary amine **I** iii) amidification of **I**, iv) cyclisation step in presence of **H** v) cleavage of TBDMS protective group with TBAF. Then, the dialkylation step give us the desired dioxopiperazine **B** with the right configuration and an excellent diastereoselectivity, higher than 95% (NMR ^1H). Unfortunately the yield of the reaction never exceeded 35% after optimizations. Then an hydroboration followed by an hydrolysis allowed us to obtain diol **M**. Due to the high polarity of **M** (soluble only in water) we were not able to proceed with the Mitsunobu reaction.



$[\alpha]_D^{22}$= +43 (c 0,31; H_2O)
ed > 95%

We developed then another straightforward way (way 2) to synthesize the diol **F** protected by two Boc groups in five steps with a 10% global yield: i) intramolecular cyclisation under microwaves, ii) coupling of two pyroglutamic acid **D** with pyridine and acetic anhydride, iii) opening of the pyrrolidine cycles of **E** and esterification of the acid groups, catalyzed by sulfuric acid, iv) protection of the amides with Boc_2O and v) reduction of ester functions into alcohol. The next steps (Mitsunobu, Deprotection and acetylation, Hydrogenolysis) are in progress. We also synthesized a 3,6-disubstituted analogue of RA with two catechols as chelating groups in 4 steps with a 15% global yield.

Conclusion

In this work, an enantiopure synthetic and straightforward route to prepare the disubstituted dioxopiperazine **RA** and analogues has been investigated (Way 1). This asymmetric alkylation strategy is based on the activation of two *S*-phenylglycinol chiral inductors. At this time we have synthesized the key-intermediate **A** in 35% global yield and we have obtained the dialkylated product, with an excellent diastereoselectivity. The second way (Way 2) allowed us to obtain a first analogue. We also synthsized the diol F which should lead us to RA soon.

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